REMARKS

Favorable reconsideration is respectfully requested.

The claims are 15 to 29.

The above amendment defines the disease being treated in claims 19 to 21 with greater specificity. Support is evident from the disclosure on page 1, second paragraph of the present specification.

Further, new claims 25 to 29, which depend on claims 15, 18, 19, 20 and 21, respectively are presented. In these claims, the protein is defined as "casein" and the sugar is defined as "lactose".

Claim Rejection 35 U.S.C. § 112, first and second paragraphs

The Official Action states that the invention only provides the description of browning reaction products made from specific proteins and sugars, for example casein and lactose etc., and no description regarding any other browning reaction products is disclosed.

However, the present specification includes many working examples wherein variety of proteins and sugars of varied origin are subject to the browning reaction and *Helicobacter pylori* adhesion inhibiting activity of the obtained products are demonstrated. The working examples are more than sufficient to provide adequate written description and evidence of possession of the claimed invention.

The Maillard reaction (i.e. the browning reaction of sugar and protein) is a chemical reaction between sugar and protein. In the Maillard reaction, reactive carbonyl group of the sugar reacts with the nucleophilic amino group of the protein, and the sugars and proteins are polymerized to form molecules having a range of molecular weight. In view of the nature of the product of the browning reaction, it was common knowledge in the art that the biological activity, such as *Helicobacter pylori* adhesion inhibiting activity essentially does not depend on the types of sugar and protein employed.

This rejection is clearly inapplicable to claims 25 to 29 which recite specific sugars and proteins.

The rejection also states that the specification only provides the description of *Helicobacter pylori* adhesion assay and eradication test, but that no description of *Helicobacter pylori* associated disease, such as stomach cancer, is disclosed.

This rejection is overcome by the above amendment specifying diseases being treated. It was common knowledge in the art that gastritis, gastric ulcer and duodenal ulcer associated with *Helicobacter pylori* could be treated by inhibiting adhesion or eradication of *Helicobacter pylori*, as evidenced by Hosking et al. (THE LANCET, Vol. 343, Feb. 26, 1994) and Sung et al. (THE NEW ENGLAND JOURNAL OF MEDICINE, Vol. 332, No. 3, Jan. 19, 1995), copy enclosed. Hosking et al. has demonstrated that duodenal ulcer can be healed by eradication of *Helicobacter pylori* without anti-acid treatment (please see Summary). Sung et al. has demonstrated that anti-bacterial therapy without acid suppression heals the ulcers (please see Abstract).

Claim Rejection 35 U.S.C. § 103(a)

Claims 15 to 24 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (U.S. 6,329,002) and Kim et al. (U.S. 6,627,238). The rejection states that Kim et al. (U.S. 6,329,002) teach a method of preventing and/or treating disorders associated with infection by *Helicobacter pylori* with nutritional food in combination with an active strain of a living microorganism, and that anyone who eats a toast bagel (nutritional food) with cream cheese (lactic acid origin, contains living microorganism) (animal proteins derived from milk) reads on treating disorders associated with infection by *Helicobacter pylori*.

The rejection is untenable.

In the first place, Kim et al. (U.S. 6,329,002) and Kim et al. (U.S. 6,627,238) describe nothing about a toast bagel. Kim et al. (U.S. 6,329,002) describe the cream cheese not as a substance including a living microorganism but as a nutritional food (see claims 8 and 12). In this context, Kim et al. (U.S. 6,329,002) only disclose a conventional food of lactic acid origin (i.e. cream cheese) in combination with the specific active strain of living microorganism (i.e. Lactococcus sp. HY 49, Lactobacillus casei HY 2782 and Bifidobacterium longum HY 8001).

It is clear that the specific active strain of living microorganism (Lactococcus sp. HY 49, Lactobacillus casei HY 2782 and Bifidobacterium longum HY 8001) is indispensable for the invention disclosed in Kim et al. (U.S. 6,329,002) (see column 4, lines 17-36). In fact, it is demonstrated in Example 6 that control group (fed yogurt only) does not show effective prevention (please see Fig. 1).

In addition, the specific strain of living microorganism should be active in the invention of Kim et al. (U.S. 6,329,002). That is, Kim et al. (U.S. 6,329,002) never teach or suggest to heat

any food. Also, it is described that "it is a general object of this invention to provide a food for general human consumption, comprising a food stored at temperature in the range of about -45°C but no more than 45°C" (see column 4, lines 37-40). Therefore, Kim et al. (U.S. 6,329,002) does not teach or suggest anything about the product of browning reaction.

Claims 15 to 24 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (US. 6,329,002), in view of Kim et al. (U.S. 6,627,238), and further in view of Kodama et al. (U.S. 2001/0044120).

This rejection is also respectfully traversed.

Kodama teaches nothing of a browning product of a protein and a sugar. A browning product as presently recited and glycoprotein such as that of Kim are very different products as explained in the response of March 22, 2007 and the accompanying Declaration. Therefore, Kodama does not overcome the above-discussed deficiencies of the Kim references.

For the foregoing reasons, it is apparent that the rejections on prior art are untenable and should be withdrawn.

No further issues remaining, allowance of this application is respectfully requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact undersigned at the telephone number below.

Respectfully submitted,

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Duodenal ulcer healing by eradication of *Helicobacter pylori* without anti-acid treatment: randomised controlled trial

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Summary

Randomised trials have shown that duodenal ulcers treated by H_2 blockers heal faster if *Helicobacter pylori* is eradicated concurrently. It remains unknown whether eradication of *H pylori* without suppression of acid-secretion, is sufficient to allow healing.

153 patients with *H pylori* infection and duodenal ulcer were randomised to receive either a 1-week course of bismuth subcitrate, tetracycline, and metronidazole (76), or omeprazole for 4 weeks with the same three-drug regimen for the first week (77). Endoscopy and antral biopsies were done at entry and 4 weeks after treatment. 132 patients were suitable for analysis. Duodenal ulcers healed in 60 (92%; 95% CI 86–100%) patients taking bismuth, tetracycline, and metronidazole compared with 63 (95%; 88–100%) taking omeprazole in addition to the three other drugs. *H pylori* was eradicated in 61 (94%; 88–100%) who received only three drugs compared with 66 (98%; 96–100%) who received omeprazole as well. Symptoms were reduced more effectively during the first week in patients who received omeprazole ($p=0.003$).

We conclude that a 1-week regimen of bismuth, tetracycline, and metronidazole for patients with *H pylori* and duodenal ulcer eradicates the organism and heals the ulcer in most patients. Concurrent administration of omeprazole reduces ulcer pain more rapidly but has no effect on ulcer healing.

Lancet 1994; **343:** 508–10

Introduction

For most of the last 70 years, methods of healing duodenal ulcers have relied on reduction of gastric acid. Recently, other factors including mucosal prostaglandins, pepsin, and the mucous layer have been implicated in duodenal ulcer and the pharmacodynamics of drugs such as misoprostil[1] confirm this. The link between *Helicobacter pylori* and duodenal ulcer indicates another—possibly the most important—factor in the causes of this disease. Several randomised trials[2-4] have shown that provided *H pylori* is eradicated, the relapse rate of duodenal ulcer is reduced from around 85% to 5–10% in the following year. Studies have shown that duodenal ulcers treated with H_2 blockers heal faster if *H pylori* is eradicated concurrently.[5,6] It remains unknown whether eradication of *H pylori* alone, without acid suppression, is sufficient to heal duodenal ulcers. If so, this would provide further evidence of a causal link between *H pylori* and duodenal ulcer. We did a randomised trial to test this hypothesis.

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Patients and methods

All patients coming to the Prince of Wales Hospital between Nov 1991, and Sept 1992, with dyspepsia and found to have an endoscopically proven duodenal ulcer, were entered into our trial unless they were aged under 16 or over 75 years, had a history of gastrointestinal bleeding within the previous 4 weeks, had had previous acid-reduction surgery, were pregnant, or intended to leave Hong Kong within 5 weeks of starting treatment. Eligible patients had antral biopsies for urease activity (CLO test, Delta West, Western Australia), microscopy, and culture to detect *H pylori*. Patients were considered to be *H pylori* positive or *H pylori* negative based on the results of culture. All positive cultures were tested for sensitivity to tetracycline and metronidazole. Our laboratory techniques have been published elsewhere.[7] Patients were randomised by instructions in sealed envelopes to receive either a 1-week course of bismuth subcitrate 120 mg, tetracycline 500 mg, and metronidazole 400 mg (BTM) four times per day, or the same regimen for 1 week plus omeprazole 20 mg per day for 4 weeks (OBTM); all treatments starting on the day of randomisation. The average duration and severity of each patient's symptoms during the week before first endoscopy were recorded. Each patient was then given a diary card to record symptoms during the next 5 weeks. After 1 week of treatment, all patients were interviewed by a research nurse to check on drug compliance, side effects, and ulcer symptoms. Patients randomised to receive 1 week's treatment of BTM alone were then given 60 antacid tablets (neutralising capacity 11·5 mmol acid per tablet) to be taken as required. Delaying antacid ingestion until after the first week was to prevent possible interaction between these and the antibiotics.

5 weeks after trial entry (4 weeks after stopping anti-*H pylori* treatment), patients returned their diary cards and remaining tablets, and underwent further endoscopy and tests as described above. The endoscopist and microbiologist were unaware of the patient's randomisation. Patients gave informed consent and the trial was approved by the Prince of Wales Hospital ethical committee.

Statistics

Trial size was calculated by assuming a healing rate of 95% for patients given OBMT. 150 patients were required to show with a power of 99% that healing rates were within 10% of each other. Allowing for dropouts and exclusions, 160 patients were randomised. Comparability between the two groups of patients was tested by χ^2 analysis, symptoms were compared by Mann-Whitney U test, and results of ulcer healing were analysed by Fisher's exact test.

Results

160 patients with duodenal ulcer were randomised (table 1). The two groups were well matched with respect to age and sex. Pretreatment symptoms were worse in the group of patients who took omeprazole and there were more smokers in this group but neither difference was significant ($p=0.06$ and 0·11, respectively). No patients were taking

	Omeprazole, bismuth, tetracycline, and metronidazole	Bismuth, tetracycline, and metronidazole
No	80	80
Median age (range)	46 (22–74)	44 (17–75)
Males	48 (60%)	50 (62%)
Smoker	23 (29%)	12 (15%)

Table 1: **Demographic details of patients randomised**

	Omeprazole, bismuth, tetracycline, and metronidazole	Bismuth, tetracycline, and metronidazole
H pylori absent at entry	3	4
Poor compliance due to side effects	5	5
Drugs lost	0	2
Wrong diagnosis	1	0
Intercurrent illness	1	0
Defaulted follow-up	3	4
Total	13	15

Table 2: **Patients excluded after randomisation**

nonsteroidal anti-inflammatory drugs, none had received anti-*H pylori* treatment previously, and none had received treatment for their ulcer in the week before trial entry. 28 patients (13 patients taking OBTM and 15 patients taking BTM) were excluded after randomisation (table 2) and 132 patients completed the trial.

Endoscopy done 4 weeks after cessation of treatment showed that duodenal-ulcer healing was almost the same in the two groups; 63 (94%; 95% CI 88–100%) of 67 patients who received OBTM had healed ulcers as did 60 (92%; 86–100%) of 65 patients who received BTM. Eradication of *H pylori* was achieved in 66 (98%; 96–101%) patients who received OBTM compared with 61 (94%; 88–100%) who received BTM (table 3). During the first week of treatment, symptoms were relieved more effectively in patients taking OBTM than in those taking BTM. Patients who took OBTM had a mean of 2·9 days (2·3–3·5) during which they had pain compared with 4·2 days (3·6–4·8) for patients who received BTM. Subsequently, the number of days during which patients had pain was similar (table 4). 48 of the 65 who received BTM took antacids during weeks 2–5; the median number of tablets taken was 17 per patient. On an intention-to-treat basis (excluding those who were *H pylori* negative at the outset), ulcer healing occurred in 91·7% (85·3–98·1%) of OBTM patients and 92·8% (86·6–98·9%) of BTM patients. Eradication of *H pylori* was achieved in 98·6% (95·9–100%) of patients who received OBTM and 91·3% (84·7–98·0%) of patients who received BTM. During the first week of treatment, patients who took OBTM had 2·8 days (2·3–3·4) of pain compared with 4·3 days (3·7–4·8) for those who took BTM.

The results of testing for *H pylori* after treatment showed complete agreement between smear microscopy, culture, and presence of urease in all but 2 patients (1 false-negative urease, 1 false-negative smear). All isolates were sensitive to tetracycline. 17 were sensitive to metronidazole; a further

	Omeprazole, bismuth, tetracycline, and metronidazole	Bismuth, tetracycline, and metronidazole
Duodenal ulcer		
Healed	63	60
Unhealed (*H pylori* positive)	4 (0)	5 (1)
H pylori		
Eradicated	66	61
Not eradicated	1	4

Table 3: **Endoscopic and biopsy results at completion of trial**

	Omeprazole, bismuth, tetracycline, and metronidazole	Bismuth, tetracycline, and metronidazole
No	67	65
Mean number of pain days		
During first week after entry	2·9*	4·2*
During 2nd–5th week after entry	5·5	6·6
Side effects of treatment	4	4

*p=0·003.

Table 4: **Symptoms during treatment of patients completing the trial**

52 had reduced sensitivity and 63 were resistant. Isolates obtained from all 5 patients in whom *H pylori* was not eradicated showed no difference in metronidazole sensitivity from pretreatment isolates; isolates were resistant to metronidazole in 4.

Discussion

Our trial provides evidence that eradication of *H pylori* allows duodenal ulcers to heal without the need for additional ulcer-healing treatment. The trial was not conducted in a double-blind manner. Because the major end points (ulcer healing and *H pylori* eradication) are objective, we did not feel it necessary to blind patients to the medication. Follow-up endoscopy and the laboratory tests were, however, done by personnel unaware of the treatment. Our trial supports the hypothesis that *H pylori* and duodenal ulcer are linked causally rather than by association and confirms that *H pylori* is an important factor in the pathogenesis of duodenal ulcer.

Randomised trials have already shown that eradicating *H pylori* reduces ulcer recurrence.[2] In these trials, ulcer healing (achieved by H_2 blockers or 4–6 weeks of bismuth) occurred independently of whether *H pylori* was cleared. Nonetheless, several studies have suggested that eradication *H pylori* not only prevents ulcer recurrence but also aids ulcer healing. Zheng et al[8] randomised 70 patients with peptic ulcer (57 duodenal) to receive furazolidine alone for 2 weeks or placebo. Ulcer healing (all types) occurred in 73% and 24% of patients, respectively, after 2 weeks of treatment. *H pylori* status was not recorded. Graham et al[5] randomised 105 patients with duodenal ulcer to receive ranitidine plus bismuth, tetracycline, and metronidazole, or ranitidine alone. After 4 weeks, 74% and 53% of patients, respectively, had healed ulcers; after 16 weeks these figures rose to 98% and 84%, respectively. Since *H pylori* was eradicated in most patients who received triple therapy, the authors concluded that anti-*H pylori* treatment may be particularly useful for the patient with resistant ulcer. Wagner et al[6] studied 59 patients with ulcers which remained unhealed after 6 weeks' treatment with an H_2 blocker. Patients received either bismuth or ranitidine, or both, until their ulcer healed. After 8 weeks, greatest ulcer healing occurred in patients who had taken bismuth. In this group, eradication of *H pylori* was associated with 86% of ulcers healing compared with 65% if *H pylori* persisted. Since 8 weeks' treatment with bismuth can heal ulcers without eradicating *H pylori*, it is difficult to assess how important the eradication of *H pylori* was in these patients with resistant ulcers.

Our choice of drugs was based on a previous study[7] in which *H pylori* was eradicated in 94% of patients given this 1-week anti-*H pylori* regimen. It could be argued that since bismuth heals ulcers independently of its anti-*H pylori* action, its inclusion confuses our results. This seems unlikely since we gave bismuth for only 1 week; previous

studies show that ulcer healing following 2 weeks of bismuth treatment is 35%,[9] after 4 weeks is 84–90%, and only reaches 97–100% after 8 weeks.[10,11] No antacids were given in the first week to any patient because both omeprazole[12] and bismuth[10] reduced ulcer pain. We also wished to avoid possible antacid interactions with tetracycline. Our subsequent use of antacids in BTM patients only was based on evidence that omeprazole abolishes ulcer pain within 7 days in the majority of patients and therefore antacids would not be needed in patients receiving omeprazole for 4 weeks. Our results showed that omeprazole plus BTM abolished ulcer pain more rapidly than BTM during the first week. In subsequent weeks the number of days during which pain was experienced was similar in both groups of patients.

Side effects from our regimen resulted in 10 patients failing to take all the treatment and a further 8 reported mild side effects but finished treatment. Previous attempts to find a more simple and effective regimen that eliminates *H pylori* have invariably resulted in lower eradication rates. Omeprazole with amoxicillin has been investigated but the results are variable. Eradication appears to be proportional to the dose of omeprazole used, being about 30% when 20 mg per day is taken,[13] 50% with 40 mg per day,[14] and rising to 80% for 80 mg per day.[15] In the last study, side effects were infrequent but the duration of treatment was 7½ weeks. Previous studies have shown the minimum inhibitory concentration (MIC) for amoxicillin against *H pylori* to be directly related to pH; a low pH necessitates a higher MIC.[16] The same studies showed that the activities of metronidazole and tetracycline against *H pylori* were less dependent on pH. This may partly explain why our regimen (which contained tetracycline rather than amoxicillin) was effective in eradicating *H pylori* regardless of whether acid had been suppressed by omeprazole.

Patients with bleeding ulcers were excluded from this study. We have already observed that only 73% of patients with bleeding ulcers have *H pylori* compared with 95–100% of patients with non-bleeding ulcers.[7] We believe our BTM regimen would be safe in patients who had bled provided that *H pylori* was confirmed, since neither omeprazole nor H_2 blockers have been shown to affect early rebleeding rates[17] and their omission would therefore make little difference to the final outcome.

Routine eradication of *H pylori* in patients with duodenal ulcer to prevent recurrence has been viewed with reservation for a number of reasons. These include lack of chronicity in some patients, side effects of treatment, ulcers due to nonsteroidal anti-inflammatory drugs, the proven safety of long-term antisecretory agents, and the appearance of bacteria resistant to antibiotics. Resistance to metronidazole has been argued as a reason for failure of treatment. Logan et al reported metronidazole resistance in 70% of pretreatment isolates and 100% of post-treatment isolates from patients in whom *H pylori*-eradication treatment had failed.[18] However, 19% of resistant isolates were eradicated by their metronidazole-containing regimen. In another large study, 27% of patients with isolates resistant to metronidazole were cleared of *H pylori* by a regimen of triple therapy.[19] We agree that treatment failure is more likely to be associated with metronidazole resistance, but would stress the poor negative predictive value of such resistance with respect to eradication. Factors that determine success of treatment other than in-vitro antibiotic sensitivity have yet to be identified.

We conclude that duodenal ulcers associated with *H pylori* will heal without acid suppression if *H pylori* is eradicated. This approach is recommended for patients in whom both ulcer healing and eradication of *H pylori* are required. Combining omeprazole with triple therapy reduces ulcer pain more rapidly, but since it has no additional effect on ulcer healing, administration for more than 1 week appears to be unnecessary.

We thank Miss P Y L Yiu for technical support and Dr Joseph T F Lau for statistical advice.

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ANTIBACTERIAL TREATMENT OF GASTRIC ULCERS ASSOCIATED WITH *HELICOBACTER PYLORI*

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Abstract *Background.* There is a strong association between infection with *Helicobacter pylori* and gastric ulcers that are unrelated to the use of nonsteroidal antiinflammatory medications. We studied the efficacy of antibacterial therapy without medication to suppress gastric acid for the treatment of patients with *H. pylori* infection and gastric ulcers unrelated to the use of nonsteroidal agents.

Methods. Patients with gastric ulcers seen on endoscopy and with *H. pylori* infection confirmed by smear or culture were randomly assigned to receive either a one-week course of antibacterial agents (120 mg of bismuth subcitrate, 500 mg of tetracycline, and 400 mg of metronidazole, each given orally four times a day) or a four-week course of omeprazole (20 mg orally per day). Follow-up endoscopies were performed after five and nine weeks. The patients and their physicians were aware of the treatment assignments, but the endoscopists were not.

Results. A total of 100 patients were randomly assigned to treatment, and 85 completed the trial. At five weeks, *H. pylori* had been eradicated in 41 of the 45 patients in the antibacterial-treatment group (91.1 percent; 95 percent confidence interval, 82.9 to 99.3) and in 5 of the 40 in the omeprazole group (12.5 percent; 95 percent confidence interval, 2.3 to 22.7; $P<0.001$). The gastric ulcers were healed in 38 of the patients treated with antibacterial drugs (84.4 percent; 95 percent confidence interval, 73.9 to 95.0) and in 29 of those treated with omeprazole (72.5 percent; 95 percent confidence interval, 58.6 to 86.4; $P=0.28$). At nine weeks, ulcer healing was confirmed in 43 of the patients receiving antibacterial therapy and in 37 of those receiving omeprazole ($P=1.0$). The mean (±SD) duration of pain during the first week of treatment was 1.9±2.6 days in the omeprazole group, as compared with 3.6±3.0 days in the antibacterial-treatment group ($P=0.004$). One year after treatment, recurrent gastric ulcers were detected in 1 of 22 patients (4.5 percent) in the antibacterial-treatment group and in 12 of 23 (52.2 percent) in the omeprazole group ($P=0.001$). *H. pylori* was detected in the 1 patient with a recurrent ulcer who had received antibacterial treatment and in 10 of the 12 patients with recurrent ulcers who had received omeprazole.

Conclusions. In patients with *H. pylori* infection and gastric ulcers unrelated to the use of nonsteroidal antiinflammatory drugs, one week of antibacterial therapy without acid suppression heals the ulcers as well as omeprazole and reduces the rate of their recurrence. (N Engl J Med 1995;332:139-42.)

ABOUT 70 percent of patients with gastric ulcers are infected with *Helicobacter pylori*.[1,2] The use of nonsteroidal antiinflammatory drugs does not increase susceptibility to infection with *H. pylori*.[3,4] Most gastric ulcers that are not related to treatment with these antiinflammatory drugs are accompanied by antral gastritis and *H. pylori* infection, whereas about 50 percent of gastric ulcers associated with these medications are not accompanied by *H. pylori*–associated gastritis.[5] If patients with ulcers induced by nonsteroidal antiinflammatory drugs are excluded, the prevalence of infection with *H. pylori* in patients with gastric ulcers is around 96 percent.[6] A strong association, however, does not establish a causal relation between *H. pylori* infection and gastric ulcer disease.

In a previous study, we found that duodenal ulcers healed as well after the eradication of *H. pylori* with antibacterial therapy as they did after treatment with both antibacterial therapy and medication to suppress gastric acid.[7] In this study, we investigated the efficacy of antibacterial therapy for the treatment of *H. pylori*–associated gastric ulcers after excluding cases related to the use of nonsteroidal antiinflammatory drugs. Our hypotheses were that gastric ulcers not associated with these medications are causally related to *H. pylori* infection and that antibacterial therapy without additional medications can heal these ulcers and reduce the likelihood of their recurrence.

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METHODS

All patients presenting to the Prince of Wales Hospital with dyspepsia or epigastric pain who were found to have gastric ulcers by endoscopy were eligible for the study. Patients were excluded if they were under 16 years of age, had used nonsteroidal antiinflammatory drugs in the previous three months, had had gastrointestinal bleeding within the previous four weeks, had previously undergone surgery to reduce gastric acid, or had received antibacterial therapy in the past. A gastric ulcer was defined endoscopically as a breach of the mucosa with a well-defined ulcer crater. Antral biopsies as well as biopsies around the gastric ulcers were performed to test for urease activity (Campylobacter-Like Organism [CLO] test, Delta West, Western Australia), with Gram's-stain smears and cultures to detect *H. pylori*. Patients were considered to be positive for *H. pylori* if either the culture or the smear from either the antral biopsy or the biopsy around the ulcer was positive. A positive result on the CLO test alone was not considered a sufficient criterion for a patient to be classified as positive for *H. pylori*. Patients initially classified as positive for *H. pylori* on the basis of the CLO test were reclassified as negative if the result of the CLO test was not confirmed by positive smears or cultures. The size of the ulcer was measured with an endoscopic ruler during endoscopy.

Patients were randomly assigned to one of two treatment groups with the use of sealed envelopes that contained the assignments. Treatment assignments were determined with a list of random numbers generated by computer. Both the patients and their physicians were aware of the treatment assignments, but the endoscopists were not.

Patients were assigned to receive either a course of bismuth subcitrate (120 mg), tetracycline (500 mg), and metronidazole (400 mg), with each medication given orally four times per day for one week, or omeprazole (20 mg per day given orally) for four weeks. In all cases, treatment was started on the day of randomization. A patient was assigned to treatment when the CLO test was positive. If infection was not confirmed by a positive smear or culture or both, the patient was classified as negative for *H. pylori* and excluded from the study.

The patients were given diary cards to record symptoms during the five weeks after their assignment to treatment. After one week of treatment, all patients were interviewed by a research nurse about compliance with the treatment, side effects, and symptoms related to the ulcer. Patients assigned to the one-week course of antibacterial therapy were then given 60 antacid tablets (Mylanta) to be taken as required.

Five weeks after randomization (i.e., four weeks after the completion of antibacterial therapy), the patients returned their diary cards and those in the antibacterial-treatment group returned any remaining antacid tablets. Follow-up endoscopy was performed to check the healing of the ulcers, and antral biopsies were repeated to obtain specimens for the CLO test, smear, and culture. If the ulcers were not completely healed, patients in the antibacterial-treatment group received antacid as necessary, and patients in the omeprazole group received omeprazole (20 mg daily) for four more weeks. A second follow-up endoscopy was performed at nine weeks. After nine weeks, all patients with persistent gastric ulcers were given omeprazole (20 mg daily) for four more weeks.

The study was approved by the ethics committee of the faculty of medicine at the Chinese University of Hong Kong. Written informed consent was obtained from all patients before they were enrolled in the trial.

Microbiologic Studies

Gram's staining was performed on minced tissue from two antral-biopsy specimens to detect gram-negative spiral organisms. The minced tissue was cultured on Columbia agar (Oxoid, Basingstoke, United Kingdom) supplemented with 5 percent horse blood and incubated for five days under microaerophilic conditions.[8] The presence of *H. pylori* was confirmed by morphologic analysis of the colony, Gram's staining,[9,10] and biochemical tests (for oxidase, catalase, and urease).

Statistical Analysis

The results of treatment in the two groups of patients were compared by chi-square analysis. Ulcer healing and eradication of *H. pylori* in the two groups were compared with Yates' correction or Fisher's exact two-tailed test.[11] The duration of symptoms was analyzed with the Mann–Whitney U test. Differences with a P value less than 0.05 were considered statistically significant.

Results

From May 1992 to April 1994, 100 patients with gastric ulcers associated with *H. pylori* infection were studied; 54 patients were randomly assigned to antibacterial therapy, and 46 to treatment with omeprazole. The two groups were well matched with respect to age, sex, history of smoking, and the site and size of the gastric ulcers (Table 1). Nine patients were excluded from the analysis: four assigned to receive antibacterial therapy (one each because of unconfirmed *H. pylori* infection, loss to follow-up, a concomitant duodenal ulcer, and previous therapy for helicobacter infection) and five assigned to receive omeprazole (one because of unconfirmed *H. pylori* infection and four because of loss to follow-up). Thus, the antibacterial-treatment group included 50 patients, and the omeprazole group 41.

H. pylori was identified around the gastric ulcer in all 50 patients in the antibacterial-treatment group and in the antrum in 49. Of the 41 patients in the omeprazole group, 39 had *H. pylori* in both the antrum and the ulcer. One patient had *H. pylori* in the antrum alone, and one in the ulcer alone. Five patients receiving antimicrobial therapy did not complete the course of medication because of side effects, including nausea, abdominal pain, diarrhea, vomiting, and dizziness (two of these patients were lost to follow-up). These five patients were given either H_2-receptor antagonists or omeprazole. One patient in the omeprazole group violated the protocol by taking an H_2-receptor antagonist in addition to omeprazole.

Table 1. Characteristics of 100 Patients with Gastric Ulcers and *H. pylori* Infection Assigned to Treatment with Antibacterial Drugs or Omeprazole.*

Characteristic	Antibacterial Drugs (N = 54)	Omeprazole (N = 46)
Age — yr		
Mean	56.4	56.3
Range	26–81	32–82
Sex — M/F	40/14	33/13
History of smoking — no. of patients (%)	26 (48)	24 (52)
Location of ulcer — no. of patients		
Antrum	15	14
Angularis	30	24
Pylorus	2	2
Lesser curve	5	4
Greater curve	1	1
Body of stomach	1	1
Size of ulcer — cm	0.82±0.53	0.92±0.55

*Plus–minus values are means ±SD.

Eighty-five patients (45 in the antibacterial-treatment group and 40 in the omeprazole group) completed the trial. The dropout rate (including patients lost to follow-up, those who could not tolerate the medication, and those who did not comply with the protocol) did not differ significantly between the antibacterial group (6 of 54 patients) and the omeprazole group (5 of 46, $P=0.78$). Since acid-suppressing medications given to the patients who could not tolerate antibacterial therapy affected ulcer healing, only patients who completed the assigned treatment were included in the analysis. We also conducted an intention-to-treat analysis that included the three patients who failed to finish the antibacterial therapy but returned for follow-up and the one patient in the omeprazole group who took an H_2-receptor antagonist.

Five weeks after randomization, eradication of *H. pylori* was documented in 41 of the 45 patients receiving antibacterial therapy (91.1 percent; 95 percent confidence interval, 82.9 to 99.3) and in 5 of the 40 patients treated with omeprazole (12.5 percent; 95 percent confidence interval, 2.3 to 22.7; $P<0.001$). Endoscopy at five weeks showed complete healing of the ulcers in 38 of the patients in the antibacterial-therapy group (84.4 percent; 95 percent confidence interval, 73.9 to 95.0)

Table 2. Ulcer Healing and Duration of Pain, According to Treatment Group.*

RESPONSE TO TREATMENT	ANTIBACTERIAL DRUGS	OMEPRAZOLE	P VALUE
Ulcer healing — no. of patients (%)			
Wk 5	38 (84.4)	29 (72.5)	0.28
Wk 9	43 (95.6)	37 (94.9)	1.00
Wk 13	45 (100)	38 (97.4)	0.46
Days with pain			
Wk 1	3.6±3.0	1.9±2.6	0.004
Wk 2–5	7.6±9.5	4.4±8.7	0.089

*In the antibacterial-treatment group, 45 patients completed follow-up at 5, 9, and 13 weeks. In the omeprazole group, 40 patients completed follow-up at 5 and 9 weeks, and 39 completed follow-up at 13 weeks. For details, see the text. Plus–minus values are means ±SD.

and 29 of those in the omeprazole group (72.5 percent; 95 percent confidence interval, 58.6 to 86.4; P = 0.28). One patient in the latter group was lost to follow-up after five weeks.

At nine weeks, the ulcers had completely healed in 43 of the 45 patients who received antibacterial therapy (95.6 percent; 95 percent confidence interval, 89.5 to 100) and in 37 of the 39 who received omeprazole (94.9 percent; 95 percent confidence interval, 88 to 100; P = 1.0). The four patients whose ulcers had not healed at 9 weeks were examined again at 13 weeks. The two patients in the antibacterial-treatment group had been given omeprazole for four weeks, and their ulcers were healed. One of them remained positive for *H. pylori* infection. One of the two patients in the omeprazole group had complete healing of the ulcer after a total of 13 weeks of omeprazole therapy; the other patient was referred for surgery because the ulcer remained unhealed.

The mean (±SD) duration of epigastric pain during the first week of treatment was longer in the group treated with antibacterial therapy (3.6±3.0 days) than in the group treated with omeprazole (1.9±2.6 days, P = 0.004). The duration of pain from the second to the fifth week after randomization was 7.6±9.5 days for those receiving antibacterial therapy and 4.4±8.7 days for those receiving omeprazole (P = 0.089) (Table 2).

In an intention-to-treat analysis, ulcer healing had occurred at five weeks in 40 of 48 patients assigned to antibacterial treatment (83.3 percent; 95 percent confidence interval, 72.7 to 93.9) and in 30 of 41 assigned to omeprazole (73.1 percent; 95 percent confidence interval, 59.6 to 86.7; P = 0.36). *H. pylori* had been eradicated in 41 patients in the antibacterial-treatment group (85.4 percent; 95 percent confidence interval, 75.4 to 95.4) and in 5 of those in the omeprazole group (12.2 percent; 95 percent confidence interval, 2.2 to 22.2; P<0.001). At nine weeks the ulcers had healed in 46 of the patients assigned to antibacterial therapy (95.8 percent; 95 percent confidence interval, 90 to 100) and in 38 of those assigned to omeprazole (95.0 percent; 95 percent confidence interval, 88 to 100; P = 1.0). During the first week of treatment, the mean duration of pain was 3.5±2.8 days in the antibacterial-therapy group, as compared with 2.1±2.6 days in the omeprazole group (P = 0.009). The duration of pain in the second to fifth weeks did not differ significantly between the two groups (7.3±9.6 and 4.9±8.8 days, respectively; P = 0.139).

As of August 1994, 45 patients had returned for the one-year follow-up evaluation. Recurrent gastric ulcers were detected in 1 of 22 patients in the antibacterial-treatment group (4.5 percent) and in 12 of 23 in the omeprazole group (52.2 percent, P = 0.001). *H. pylori* was detected in the 1 patient in the antibacterial-treatment group with a recurrent ulcer and in 10 of the 12 patients in the omeprazole group with recurrent ulcers (83.3 percent). In addition, duodenal ulcers had developed in two patients in the omeprazole group within one year after treatment; both were positive for *H. pylori* infection.

DISCUSSION

Most gastric ulcers occur with chronic diffuse gastric inflammation.[12] Clinical and histologic studies have suggested that *H. pylori*–related gastritis and gastric ulcer represent a continuum of progressive disease.[13,14] A causal relation between *H. pylori* infection and the development of gastric ulcers would be supported if the bacterial infection were treated successfully with antibacterial agents alone.

Graham et al. reported that among patients with gastric ulcers who were treated with three antibacterial drugs and ranitidine, the incidence of recurrent ulcers was significantly reduced after the eradication of *H. pylori*.[1] Labenz and Börsch used various combinations of omeprazole and antibiotics (amoxicillin, ciprofloxacin, and roxithromycin) to treat 83 people with *H. pylori*–associated gastric ulcers and found that the eradication of *H. pylori* enhanced the healing of the ulcers and reduced their recurrence.[15] In both studies, patients received medications that suppressed acid production. The German Gastric Ulcer Study Group randomly assigned patients with gastric ulcers to receive omeprazole or three antibacterial drugs, including eight weeks of bismuth, and found that the eradication of *H. pylori* resulted in the healing of the ulcers.[16] The Finnish Gastric Ulcer Study Group randomly assigned patients with gastric ulcers to receive bismuth (for 8 weeks) plus metronidazole (for 10 days), bismuth alone (for 10 days), or ranitidine alone (for 8 weeks)[17] and concluded that the eradication of *H. pylori* improved the healing of the ulcers and prevented relapses. In both the German and the Finnish studies, however, the healing of ulcers in the groups receiving antibacterial therapy could be attributed in part to the eight-week course of bismuth.

We compared a one-week course of three antibacterial drugs but no medication to suppress acid with a four-week course of omeprazole, a proton-pump inhibitor used as the standard treatment for ulcers. Our findings in the antibacterial-treatment group establish a link between the eradication of *H. pylori* and ulcer healing, although the possibility of spontaneous healing in some instances cannot be excluded. There was a

trend toward an increased rate of healing in the antibacterial-treatment group after five weeks. The rate of healing at 9 and 13 weeks was similar in the two groups. Our findings are very similar to those in our previous study of the use of antibacterial therapy for the treatment of *H. pylori*–associated duodenal ulcers.[7] The two studies provide evidence in support of a causal relation between *H. pylori* infection and the development of gastric and duodenal ulcers, respectively.

The relief of symptoms was significantly more rapid during the first week of treatment with the use of a medication that suppressed acid production, as compared with antibacterial therapy alone. This difference, which did not persist after the first week of treatment, was probably due to the potent acid-suppressing effect of omeprazole and the gastrointestinal side effects of treatment with three antibacterial drugs. We cannot rule out the possibility of bias in the patients' reports of symptoms, since they were not blinded to treatment. The rate of recurrent ulcers at one year was significantly higher in the omeprazole group than in the antibacterial-treatment group. Most of the patients with recurrent ulcers, including the one patient in the antibacterial-treatment group, were positive for *H. pylori* infection. Our findings are consistent with those of previous studies in which patients with gastric ulcers were treated with medication directed against *H. pylori*. These studies found that *H. pylori* infection was the most important predictor of the recurrence of ulcers.[1,13-15]

We conclude that one week of antibacterial treatment (bismuth subcitrate, tetracycline, and metronidazole) without acid suppression heals *H. pylori*–associated gastric ulcers that are unrelated to the use of nonsteroidal antiinflammatory drugs and reduces the rate of recurrence of ulcers.

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